



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: A61K 7/42, 7/06, 7/00, 31/19, 31/045, 31/07	A1	(11) International Publication Number: WO 99/51198
		(43) International Publication Date: 14 October 1999 (14.10.99)
(21) International Application Number: PCT/US99/07495 (22) International Filing Date: 6 April 1999 (06.04.99) (30) Priority Data: 09/055,274 6 April 1998 (06.04.98) US (71) Applicant (for all designated States except US): CODON PHARMACEUTICALS, INC. [US/US]; 200 Perry Parkway, Gaithersburg, MD 20877 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): REN, Wu, Yun [US/US]; 12518 Timber Hollow Place, Germantown, MD 20874 (US). SEIDMAN, Michael [US/US]; 3639 Veazey Street, N.W., Washington, DC 20008 (US). BROWN, David, A. [US/US]; 4534 Kingcup Court, Ellicott City, MD 21042 (US). (74) Agent: TARCZA, John, E.; Codon Pharmaceuticals, Inc., 200 Perry Parkway, Gaithersburg, MD 20877 (US).		(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KP, KR, LC, LK, LR, LS, LT, LV, MG, MK, MN, MW, MX, NO, NZ, PL, RO, SD, SG, SI, SK, SL, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: DERMATOLOGICAL FORMULATIONS AND METHODS		
(57) Abstract A method and dermatological formulation are provided for increasing the pigmentation response of mammalian skin, hair, wool or fur to agents which stimulate melanogenesis. The method comprises administering to mammalian skin, hair, wool or fur a dermatological formulation containing a melanogenesis-stimulating effective amount of an agent which stimulates melanogenesis in melanocytes, and a melanogenesis-enhancing effective amount of an agent, such as an α -hydroxy acid, which enhances the stimulation of melanogenesis by the melanogenesis-stimulation agent.		

DERMATOLOGICAL FORMULATIONS AND METHODS

BACKGROUND OF THE INVENTION

5

1. Field of the Invention

The present invention relates to enhancing the pigmentation response to inducers of melanogenesis by inclusion of melanogenesis-enhancing agents in formulations applied to skin, hair, wool or fur.

2. Description of the Related Art

There have been various descriptions of the use of compounds for stimulating melanogenesis or pigmentation. U.S. Patent No. 5,352,440 describes increasing melanin synthesis in melanocytes and increasing pigmentation by administration of certain diacylglycerol compounds. Increased pigmentation in mammalian skin via administration of certain DNA fragments is disclosed in U.S. Patent No. 5,532,001. U.S. Patent No. 5,554,359 is directed to increasing levels of melanin in melanocytes by administration of lysosomotropic agents. And various melanogenic diols are described in Brown et al., 1998, J. Invest. Dermatol., 110:428-427.

While certain methods and compositions for stimulating pigmentation are known, there exists a need for improvements in the art. The present invention provides improved methods and compositions for stimulating pigmentation responses in mammalian skin, hair, wool or fur.

hydroxy acids, salts and derivatives thereof; α -keto acids, salts and derivatives thereof; β -hydroxy acids, salts and derivatives thereof; retinoids, salts and derivatives thereof; Vitamin A and related compounds; acids such as trichloroacetic acid and trifluoroacetic acid; phenol; and, methoxypropyl-gluconamide.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A-1B illustrate skin pigmentation responses.

10.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

This invention is based on the unique observation that certain compounds greatly increase the pigmentation response in mammalian skin treated with agents known to stimulate melanin production in melanocytes. Thus, the present invention is useful in the treatment of hypopigmentation disorders, such as albinism, vitiligo, etc. It is also believed that increasing the pigmentation of skin according to the present invention will protect such skin from subsequent UV light damage, sunburn, photoaging and development of skin cancers.

The present invention may be used in the treatment of any mammalian skin, hair, wool or fur. Treatment of human skin is preferred.

As discussed above, the present invention provides for an increased pigmentation response by administration of a composition comprising (1) an agent which stimulates melanin

[1S,2S,3R,5S] - [+] -pinanediol); 2,3-cis/exo-bornanediol; 5-norbornene-2,2-dimethanol; norbornane-2,2-dimethanol; 2-hydroxy-2-norbornanemethanol; 1-(exo-2-norbornyl-)-propan-1,2-diol; and, 1-(endo-2-norbornyl-)-propan-1,2-diol.

5 Melanogenesis-enhancing agents according to the present invention include α -hydroxy acids, salts and derivatives thereof such as glycolic acid, lactic acid, ammonium lactate, mandelic acid, benzilic acid, malic acid, tartaric acid, gluconic acid and citric acid; α -keto acids, salts and
10 derivatives thereof such as pyruvic acid; β -hydroxy acids, salts and derivatives thereof such as salicylic acid; retinoids, salts and derivatives thereof such as tretinoin and isotretinoin; Vitamin A, Vitamin A₂ and Vitamin A aldehyde; acids such as trichloroacetic acid and
15 trifluoroacetic acid; phenol; and, methoxypropyl-gluconamide. The aforementioned compounds possess properties such as the ability to diminish epidermal corneocyte cohesion, reduce stratum corneum thickness, stimulate keratinocyte proliferation, increase epidermal
20 thickness, result in more even distribution of melanocytes, result in more even distribution of melanin, and to stimulate dispersal of melanin. Any melanogenesis-enhancing agent may be used as long as it enhances the ability of a melanogenesis-stimulating agent to increase melanin
25 production by melanocytes. Alpha-hydroxy acids are the preferred melanogenesis-enhancing agent.

Alpha-hydroxy acids have not been reported to possess melanogenic ability. In fact, α -hydroxy acids have been

melanocytes, but also proliferation of keratinocytes such that transport of melanin through the epidermis is enhanced (Jimbow, K., et al., 1991. Biochemistry and physiology of melanin production, pages 873-909, In: Physiology, Biochemistry, and Molecular Biology of the Skin, L. A. Goldsmith, ed. Oxford University Press, New York, USA.; Jimbow, K., et al., 1993. Biology of melanocytes, pages 261-289, In: Dermatology in General Medicine, Volume 1, Fourth Edition, T.B. Fitzpatrick et al., ed. McGraw-Hill, Inc., New York). Melanogenic diols act directly on melanocytes to stimulate melanogenesis (Brown et al., 1997, J. Invest. Dermatol., In Press), but there is no evidence to indicate that melanogenic diols stimulate proliferation of human keratinocytes. Thus, they may stimulate only part of the physiological response necessary for effective tanning.

It is contemplated that melanogenesis-enhancing agents, e.g., α -hydroxy acids, complete the requirements for effective tanning by stimulating the proliferation of keratinocytes and thereby facilitating the distribution of melanin throughout the epidermis. Furthermore, the reduced clumping of melanin and increased dispersal of melanin which are enhanced by α -hydroxy acids are well-known features of darkly pigmented skin (Jimbow, K., et al., 1993. Biology of melanocytes, pages 261-289, In: Dermatology in General Medicine, Volume 1, Fourth Edition, T. B. Fitzpatrick et al., ed. McGraw-Hill, Inc., New York).

It is further contemplated that all agents which are presently used for repair of photoaging and/or stimulation

The dose regimen will depend on a number of factors which may readily be determined, such as severity and responsiveness of the condition to be treated, but will normally be one or more doses per day, with a course of treatment lasting from several days to several months, or until a cure is effected or a diminution of disease state is achieved, or a cosmetically desired degree of melanogenesis (tanning) is achieved, depending on the application. One of ordinary skill may readily determine optimum dosages, dosing methodologies and repetition rates. In general, it is contemplated that topical formulations (such as creams, lotions, solutions, etc.) will have a concentration of melanogenesis-stimulating agent of from about 0.01% to about 50%, preferably from about 0.1% to about 10%.

It is contemplated that melanogenesis-enhancing agents will be used at concentrations which diminish epidermal corneocyte cohesion, reduce stratum corneum thickness, stimulate keratinocyte proliferation, and increase epidermal thickness, without resulting in the phenomena known as "chemical peeling" (Piacquadio, D., et al., 1996, Dermatol. Surg. 22:449-452). As such, the effective concentrations of melanogenesis-enhancing agents are expected to be in the range of 5% to 25% by weight (Stiller et al., 1996, Arch. Dermatol. 132:631-636; Ditre et al., 1996, J. Am. Acad. Dermatol. 34:187-195). However, in some cases where reparation of photodamaged skin is desirable prior to induction of pigmentation (tanning), it is contemplated that much higher concentrations of melanogenesis-enhancing agents

background; +0.25 = slight darkening, indistinct; +0.5 = slight darkening, distinct; +1 = slight-moderate darkening; +2 moderate, even darkening; +3 = substantial, even darkening; +4 = profound, even darkening.

5 When evaluated for pigmentation response 5 days after the cessation of applications, the location where Solution #1 was applied (Figure 1 A) exhibited moderate even darkening (pigmentation rating =2), while the spot where Solution #2 was applied (Figure I B) exhibited slight to
10 moderate darkening (pigmentation rating = 1). In a previous experiment in which 10 μ l 2,3-R-pinenediol dissolved in 100% ethanol was applied to the same subject 3-8 times per day for 6 days, the maximum pigmentation response obtained was slight darkening (pigmentation rating =0.5). These findings
15 show that inclusion of α -hydroxy acid in formulations results in 4-fold enhancement of the pigmentation response induced by 2,3-R-pinenediol.

Pigmentation of the location where Solution #1 was applied became apparent approximately 2 days after the final
20 day of application. Pigmentation response where Solution #1 was applied exhibited the following temporal pattern of pigmentation:

melanogenic diols), and α -hydroxy acids which stimulate proliferation of keratinocytes with resultant melanin mobilization, that results in marked induction of skin pigmentation or sunless tanning. Further, it is contemplated that this combination of stimulation of melanin production in melanocytes, and stimulation of keratinocyte proliferation in epidermis, parallels the major physiological responses involved in the natural tanning process induced by solar irradiation.

10

5. The method according to claim 1, wherein the dermatological formulation is administered to human skin.

6. The method according to claim 1, wherein the melanogenesis-stimulation agent comprises 2,3-R-pinanediol.

7. A dermatological formulation for increasing the pigmentation response of mammalian skin, hair, wool or fur to agents which stimulate melanogenesis, comprising a melanogenesis-stimulating effective amount of an agent which stimulates melanogenesis in melanocytes, and a melanogenesis-enhancing effective amount of an agent which enhances the stimulation of melanogenesis by the melanogenesis-stimulating agent.

15

8. The formulation according to claim 7, wherein the melanogenesis-enhancing agent is selected from the group consisting of α -hydroxy acids, salts and derivatives thereof; α -keto acids, salts and derivatives thereof; β -hydroxy acids, salts and derivatives thereof; retinoids, salts and derivatives thereof; Vitamin A and related compounds; acids; phenol; and, methoxypropyl-gluconamide.

9. The formulation according to claim 7, wherein the melanogenesis-enhancing agent comprises α -hydroxy acids.

10. The formulation according to claim 9, wherein the α -hydroxy acid is selected from the group consisting of

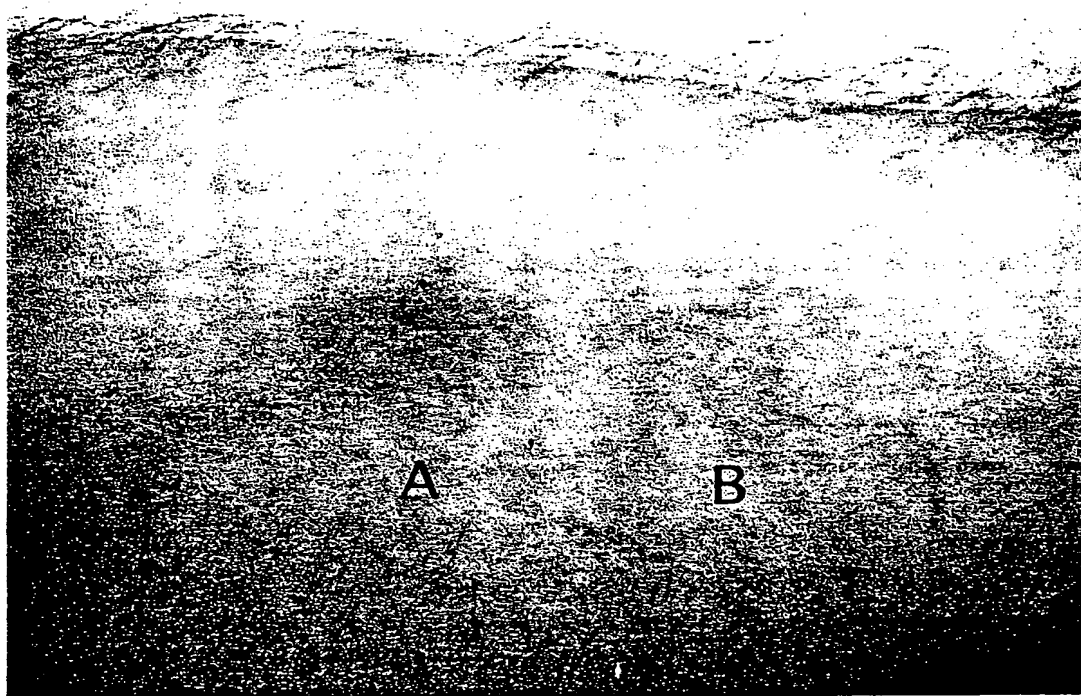


Figure 1

BEST AVAILABLE COPY